Pediatric Wegener’s granulomatosis with oral ulcers and progressive periodontitis: a case report

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Wegener’s granulomatosis (WG) is a rare multisystem disorder. Although it can occur at any age, it is rarely observed in children. Oral manifestations, which are present in fewer than 10% of patients, include oral ulceration, non-healing extraction sockets, and the most common oral lesion, hyperplastic gingivitis, which is known as “strawberry gingivitis.” We report the unusual case of a 6-year-old boy with WG who presented with atypical oral manifestations, including severe progressive periodontitis accompanied by oral ulcers, before the development of systemic symptoms. Although WG is rare, this case emphasizes the importance of considering the diagnosis in those who present with progressive and atypical oral disease, as prompt treatment of the systemic illness can significantly improve outcome. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e1-e5)

CASE REPORT

A 6-year-old boy presented with loosening of his teeth. His mother had first noticed the problem 2 years earlier. Intraoral examination revealed extensive mobility of all primary teeth. As can be seen in Fig. 1, the Primary mandibular central incisors had been replaced by the permanent central incisors. A presumptive diagnosis of early-onset periodontitis was made. Symptoms were treated and routine follow-up was advised.

The patient presented again 10 months later, complaining of “sore gums” associated with painful mucosal ulcers, which had been present for some time. On examination, it was noted that the lower first primary molars were missing, although the normal shedding time is approximately 10 years of age. In addition, the gingiva were erythematous and hyperplastic, with pseudopocketing. Two deep ulcers with pseudomembranes and purulent secretions were observed on the left soft palate, and diffuse clusters of nonspecific ulcerations were seen throughout the oral mucosa (Fig. 2).

Radiographs revealed severe horizontal alveolar bone absorption in the entire dentition, with the canine and molar areas displaying such extreme alveolar bone loss that only the apical third of the root remained supported (Fig. 3). Blood examination revealed an elevated leukocyte count (27.9 × 10^9/L) and elevated neutrophil granulocyte count (10.6 × 10^9/L) and ratio (74%). The red blood cell count was 4.29 × 10^{12}/L, hemoglobin 115 g/L, and serum alkaline phosphatase (ALP) activity was greater than 200 U/L. Blood glucose was normal at 4.55 mmol/L and the human immunodeficiency virus antibody test was negative. Chest radiography revealed diffuse hyperdense changes in the mid- and upper zones of both lungs and the computed tomography scan of the lungs revealed the presence of infiltrates and nodules. The pulmonary nodules were multiple, bilateral, and cavitated (Fig. 4). Tuberculin test and sputum detection results were negative and tuberculosis was ruled out in the patient.

At this point, the patient was referred to the Department of Internal Medicine for further investigation. Anti-neutrophil cytoplasmic antibody (ANCA) test (1:10 indirect immunofluorescence) and ANCA target antigen (1:101 EUROLINE) tests
showed that the cytoplasmic staining pattern ANCA (cANCA) and proteinase 3 (PR3) were moderately positive. Myeloperoxidase (MPO) was negative. The erythrocyte sedimentation rate (ESR) value was 57 mm/h, which was higher than the reference value (0-20 mm/h), and the high-sensitivity C-reactive protein (hs-CRP) concentration was also elevated at 88.9 mg/L (normal value <5).

Examination of the palatal biopsy specimen revealed small-vessel vasculitides with local tissue necrosis, and the presence of perivascular inflammatory cell infiltrates (Fig. 5).

Based on these results, the child was diagnosed with WG. At this point, renal involvement was not thought to be present, as the renal function radioimmunoassay tests and ultrason sound examinations were all normal. The patient was initially treated with imipenem and cotrimoxazole (120 mg/d) to control pulmonary symptoms. Subsequently, immunosuppressant therapy was commenced, with an initial trial of methotrexate (5 mg/wk) and prednisone acetate (30 mg/d).

The patient was discharged 1 month later. At this point, symptoms were well controlled, the oral ulcers were healing, and the chest x-ray showed distinct improvement with only a mild inflammatory exudate present in the upper lobes. The total white blood cell count and the neutrophil granulocyte count and ratio were all normal. The hs-CRP had reduced to 0.20 mg/L, and the ESR to 20 mm/h. On dental examination, the patient’s primary molars and canines were extremely loose and were therefore extracted. A space-maintainer was applied. Daily use of chlorhexidine mouthwash was recommended.

Immunosuppressant therapy was continued for a further year. At the 1-year review, the disease process appeared to be under control (Fig. 6).

DISCUSSION

WG is a multisystem disorder that typically affects the upper and lower airways and the kidneys, but it may involve any organ. In 1990, the American College of Rheumatology (ACR) proposed that a diagnosis of WG depends on the presence of at least 2 of the following 4 criteria: (1) oral ulcerative lesions or nasal bleeding or inflammation; (2) nodules, fixed infiltrates, or cavities on chest radiography; (3) abnormal urinary sediment; and (4) granulomatous inflammation on biopsy.29 Stewart et al.2 suggested that, although oral lesions are one of the major diagnostic criteria, oral manifestations of WG appear to have been largely ignored in the medical literature. This is possibly because of either a lack of awareness or the relative infrequency of this particular clinical presentation. Oral manifestations are indeed uncommon, particularly as presenting features.
of the disease, yet they have been well described and include palatal and lingual ulceration, aphthae, and nonhealing extraction sockets.\textsuperscript{1-3} Timely recognition of these often-overlooked oral manifestations may help in the early diagnosis of WG.\textsuperscript{2} As appropriate treatment produces a good response in most cases, an awareness of the oral manifestations of WG by both dentists and physicians could significantly affect outcome for some patients.

In the case described, the 6-year-old boy, who subsequently had a confirmed diagnosis of WG, presented with oral disease, consisting of abnormally loose teeth, progressive periodontitis, and painful oral ulceration. Such extensive oral disease is highly unusual in a healthy child, and therefore an underlying systemic illness had to be considered. The early symptoms seen in this case are similar to those observed in Papillon–Lefèvre syndrome (PLS), which is an autosomal recessive genetic disorder caused by a deficiency in cathepsin C.\textsuperscript{30-32} In this syndrome, characterized by palmoplantar keratoderma with periodontitis, severe destruction of periodontium results in loss of most of the primary teeth by the age of 4 years, and most of the permanent teeth by the age of 14 years.\textsuperscript{32} In our case, PLS was excluded, as there was no evidence of hyperkeratosis and family history was negative.

A further differential diagnosis to consider is that of hypophosphatasia, particularly odontohypophosphatasia, where children also lose their primary teeth earlier than normal. Hypophosphatasia is a rare inborn error of metabolism caused by low activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP).\textsuperscript{33-36} Odontohypophosphatasia may explain some cases of “early-onset periodontitis.”\textsuperscript{34} As a result of hypoplasia of
dental cementum, premature loss of deciduous teeth occurs. The incisors are usually shed first, and occasionally almost the entire primary dentition is exfoliated prematurely. In our case, hypophosphatasia was excluded, as serum ALP activity was normal.

Other differential diagnoses include other ANCA-positive vasculitides, such as microscopic polyangiitis (MPA), Churg–Strauss syndrome, and polyarteritis nodosa. These diseases can be differentiated from WG by history, physical examination, and appropriate laboratory and histopathological studies. WG and MPA have overlapping features, but c-ANCA and PR3-ANCA are considered to be sensitive and specific markers for WG, whereas MPO-ANCA is usually associated with MPA. However, these associations are not absolute, and MPO-ANCA can be seen in WG and PR3-ANCA in MPA. The final diagnosis is based on a combination of clinical, laboratory, and histologic findings.

The etiology of WG remains unclear. Many environmental factors, including silica exposure, bacterial or viral infectious agents, and drugs, have been put forward as important in the pathogenesis of WG and other ANCA-associated vasculitides, but with little supporting evidence. There are no detailed epidemiologic data on WG worldwide. It appears that, in adults, the disease affects both sexes equally, and has a mean age of onset of 41 years. WG rarely occurs in children. Akikusa et al. reported on a predominance of females in children with WG, with a male-to-female ratio of 1:4. Cabral et al. reported that, for children with WG, the median interval from symptom onset to diagnosis is 2.7 months (range, 0–49 months), whereas the range for adults is narrower, at 4.7 to 15.0 months.

The case we described appears to be the only one reported to date of a child presenting with generalized and progressive periodontitis, in the absence of any other symptoms, who was subsequently found to have WG.

CONCLUSIONS
It is possible that the case we described may reflect a coincidental occurrence of periodontitis in a patient with WG. However, such extensive oral disease is unlikely in the absence of an underlying condition. An awareness of the oral manifestations of systemic diseases, such as WG, although rare, would facilitate earlier diagnosis and treatment, thereby improving outcome for this group of patients.

REFERENCES